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## USSR DEVELOPMENTS IN WORK ON RADIATION SICKNESS

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[Comment: During the past few months, a number of articles on the subject of radiation sickness has appeared in the USSR scientific and popular press. While the majority of these articles review foreign work dealing with the biological effects of ionizing radiation, the account which follows below refers to USSR work in this field and treats the subject from the standpoint of medical theories which are prevalent in the USSR. In accordance with these theories, the fundamental state of the nervous system and the general effects due to the action of harmful radiation on nerve receptors are emphasized. Predominant importance is attached to general as compared with local pathogenic effects, and an alleged tendency of foreign workers to overemphasize local injuries is criticized.

The following points mentioned in the article are of particular interest:

1. A statement to the effect that measures for the prophylaxis of radiation sickness are being applied more extensively in the USSR than anywhere else in the world

2. A reference to the danger of exposure to radioactive isotopes which, according to the article, are widely used in the industry

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3. Use in radiation sickness of methods which affect the nervous system, such as administration of caffeine and bromides, application of local anesthesia as a prophylactic measure, application of the novocain block and of general anesthesia as therapeutic measures, etc.

4. In the light of the importance which is attached to blood-transfusion techniques and the maintenance of blood banks in the USSR, references to the application of blood transfusions in the prophylaxis and therapy of radiation sickness

5. Administration of the USSR liver preparation antianemin (cf. Kh. Kh. Vlados et al, "New USSR Liver Preparation Antianemin," Sovremennyye Problemy Gematologii i Perelivaniya Krovi, No 30, Medgiz, Moscow, 1953, pp 269-274) and of "protein sulfate"

6. The approval given to the use of beta-mercaptoethylamine as a prophylactic agent and the rejection as valueless of the majority of other prophylactic drugs developed abroad

7. A reference to the necessity of removing victims from the zone of exposure to radiation, indicating apparently that the quantity and type of radiation are such that it cannot be easily controlled

According to a note appended by the Russian editor, the paper by Kozlova was presented at a scientific session of the State Scientific Research X-Ray -- Radiological Institute imeni V. M. Molotov.]

Radiation sickness became known soon after the discovery of X rays and the radiation emitted by radium. The first investigators who studied the biological effects of the new type of energy that had been discovered experienced radiation sickness themselves. However, the significance of radiation sickness for the human organism has been investigated most thoroughly in connection with the therapy of patients suffering from malignant neoplasms, i.e., under conditions where irradiation of large surfaces of the body of a patient with massive doses of radiant energy is required. Many observations and statistical data have demonstrated that the results of treatment are more favorable when stronger doses are applied in the region of the tumor. However, increases in the total dose produce more severe symptoms of radiation sickness. Thus the success of radiation therapy is inextricably connected with the prevention of radiation sickness and with the elimination of this sickness.

Soviet scientists reached this conclusion long ago. Nowhere are measures for combatting radiation sickness used to the extent that they are in the USSR. Blood transfusions, transfusions of plasma, and the use of various drugs make it possible to complete successfully radiation therapy in the majority of cases. However, these measures remain effective only when radiation therapy is not applied to very large volumes of normal tissues, as is necessary in the treatment of cancer of the lungs or of the esophagus. In such cases radiation therapy is accompanied by acute forms of radiation sickness and the measures for preventing this sickness are frequently inadequate. It follows that the success of radiation therapy depends directly on the effectiveness of the therapy of radiation sickness.

Of no less importance is the diagnosis, prophylaxis, and therapy of radiation sickness as applied to otherwise healthy persons, in other words, to specialists whose work involves constant exposure to small doses of ionizing radiation. At present radioactive isotopes are being used extensively in industry. In connection with this there is exposure to external radiation produced by radioactive isotopes and to internal radiation when the isotopes are absorbed by the body. Taking into consideration the diversity of the isotopes being used and the selective resorption of these isotopes by various organs, one may assume beforehand that there will be a diversity of clinical manifestations when radiation sickness affects individual organs against the background of general radiation sickness. Prophylaxis, to which particular attention is paid in the USSR, must be based, under the conditions considered at present, on a detailed and systematic investigation of changes which take place in the organism as a result of different occupational conditions.

Thanks to numerous investigations dealing with the pathogenesis and clinical aspects of radiation sickness, it became possible to collect a large amount of actual data which clarified to some extent the complex process that is involved. The most extensive information has been obtained with regard to morphological changes which occur at the expiration of a considerable time following exposure to radiation. The changes in metabolic processes have been investigated most thoroughly, while the primary reactions in the organism have been elucidated least of all.

The inadequate extent of information on the first stages of the reaction to radiation induces some investigators to consider as primary the earliest changes which can be observed with the aid of the technical means that are available in laboratories at present. These changes comprise disturbances of normal chemical processes in tissues, particularly disturbances of oxidation processes. According to this concept, the effect on the nervous system is secondary and is produced as a result of disturbances of cellular metabolism. Solution of the problem in regard to the nature of the primary reaction is important not only from the academic point of view, but also because accurate information on the subject will make it possible to outline the correct way of developing further therapeutic measures.

For instance, the following concept in regard to the mechanism of the biological action of radiation is widespread abroad. According to this concept, the action of radiation on the living substance of tissues brings about ionization of that substance with subsequent breakage of molecular bonds and changes in the normal chemical reactions. This in turn leads to a disturbance of the functioning and the morphology of cells. The development and outcome of a process of this type can depend only on the magnitude of the action of the radiation, in other words the magnitude of the dose and the intensity of the radiation. The course of the process brought about by the radiation due to the fact that it exerts an influence on some medium within the organism may not be changed under the circumstances. However, experimental and clinical observations show that the reaction of the organism to the effects of radiation takes an active course rather than the passive course as assumed by the hypothesis outlined above. Although the physical conditions of irradiation are unchanged, the subsequent reaction may manifest itself in different degrees. The differences in individual sensitivity to radiation are extensive. For instance, the single lethal dose for humans in cases of general irradiation varies between 200 and 1,000 roentgens. The differences in sensitivity depend on the initial state of the organism, which is determined by the functional state of the nervous system.

The primary role of the nervous system in the pathogenesis of radiation sickness can be demonstrated by means of experimental and clinical data. Our observations show that preliminary local anesthesia with novocain of the area being irradiated reduces the intensity of the reaction and delays its inception for several days. Thus, notwithstanding the fact that ionization has taken place, the reaction does not progress further. The sole reason for this is that a modification of the functional state of the receptors has taken place.

Investigations carried out by I. G. Spasskaya indicate that general anesthesia [literally "narcosis"] exerts the same influence on the general reaction. The general effects produced by beta radiation, which penetrates only into the surface layers of the skin, bring about the death of animals, although pathologoanatomical examinations carried out within a short time after irradiation do not show any morphological changes. The death of the animal in such cases can be explained only by acute damage to the skin receptors. It is known that the cells of the intact organism are not capable of responding with autonomous reactions; all changes which take place in them represent the result of nerve action. Ionizing radiation is no exception. As a result of its action on the organism the exteroreceptors and interoreceptors react first. The irritation is transmitted by the central nervous system along sensory nerve paths The role of these nerve paths in the process was clearly demonstrated in experimental work carried out by Ye. I. Bakin. Modification of the functioning of receptors under the influence of radiation brings about disturbances of cellular metabolism. These in turn lead to the development of the whole complex syndrome of radiation sickness.

Notwithstanding the diverse nature of ionizing radiation (alpha rays, beta rays, gamma rays, or irradiation with protons or neutrons) the mechanism of the biological action exerted by different types of radiation is the same. However, the course of the reaction and the prognosis depend on the ways and means by which the action of the radiation is exerted. Purely schematically one may divide all forms of radiation sickness into three groups: 1. the condition which develops as a result of the prolonged action of small doses of radiation emitted by external sources and whenever radioactive isotopes penetrate into the organism; 2. a general reaction exhibited by patients after local or general irradiation with therapeutic doses; 3. acute radiation sickness which arises after intensive general irradiation.

To the first group belong the sickness that develops in a person whose work is connected with exposure to constant but weak radiation. Harmful effects arise most frequently due to negligence in applying protective measures. The sickness is characterized by a slow progress and a course which extends over several years. The most pronounced and earliest symptoms are disturbances of the functions of the central nervous system. This is indicated both by subjective and objective data. The principal complaints comprise an increased tendency to get tired, irritability, headaches, absent-mindedness, and forgetfulness.

Examination of the patients indicates that there are noticeable changes in the electrocardiogram. These changes are characteristic for dystrophic modifications of the miocardia, disturbances of intraventricular conductivity, and other changes in the activity of the heart.

Changes in the morphological composition of the blood are subsequent symptoms. These changes are expressed initially in lymphocytosis. Subsequently lymphopenia, leukopenia, and thrombocytopenia develop. These observations indicate that the assumption made earlier to the effect that the functioning of the organs of hemopoiesis is interfered with first under the action of radiation, must be discarded. It follows from the investigations which have been mentioned that the functioning of the central nervous system is affected first.

Persons whose occupation exposes them to penetration of radioactive isotopes into the body develop in addition to the symptoms outlined above, changes in the mucous membranes of the nose, the nasopharynx, and the pharynx. These changes comprise loosening of the mucous membranes, edema, and hyperemia with a cyanotic cast. In later stages atrophy of the mucous membranes develops and ulceration takes place on the surface of the mucous membranes.

Changes in the organism of patients who have been subjected to radiation therapy consist, as a rule, of general phenomena such as disturbances in the equilibrium of nerve processes, nausea, loss of appetite, loss of weight, and modifications in the morphological composition of the blood and in the metabolism. Local changes produced by damage to the tissues which had been irradiated also develop. These changes comprise atrophy of salivary and lymphatic glands, pneumoscleroses, dystrophy of the miocardia, degenerative changes in the hemopoietic organs, atrophy of the skin and of the mucous membranes in the regions which had been irradiated, etc. When the treatment has been terminated, the symptoms of the general reaction disappear in the majority of patients.

The morphological composition of the blood is restored to normal last. One often observes leukopenia which continues for several years after radiation therapy has been applied. Local changes which arise as a result or irradiation are irreversible in the majority of cases and are responsible for the development of various pathological conditions. For instance, after the irradiation of the submaxillary region, the atrophy of salivary glands and of the mucous membrane of the mouth which ensue often result in disturbances of the functioning of the gastrointestinal tract. Irradiation of the chest may result in persistent disturbances of cardiac activity.

These changes must always be taken into consideration in evaluating the condition of patients who have been subjected earlier to intensive radiation therapy. Prophylaxis of radiation sickness and elimination of this condition in this group of patients aims not only at carrying out effective measures against the development of radiation sickness, but also at preventing disability which may ensue as a result of intensive application of radiation therapy.

The acute form of radiation sickness is characterized by a rapid development of this condition and the acute nature of all symptoms. Within the course of the disease one distinguishes three stages. The first stage occurs immediately after irradiation and is characterized by depression, low spirits, occasionally loss of consciousness, a drop in the arterial pressure, nausea, and vomiting. At the end of the first day lymphopenia becomes apparent. At the expiration of several hours, all of these symptoms disappear with the exception of lymphopenia which is observed during all succeeding days of the sickness. If the number of lymphocytes drops below 800 per cubic millimeter, one may assume that a very severe injury has taken place. During the succeeding days, the condition of the patients improves and returns to normal in the case of some patients.

At the expiration of two to three weeks, the second stage begins, which is characterized by a worsening of the condition of the patient. There is a rise of temperature and hemorrhagic symptoms, tumors of the mucous membrane of the nasopharynx, diarrhea, and sepsis are observed. In aggravated forms the hemorrhagic syndrome and sepsis predominate.

The third stage, that of recovery, is characterized by a slow disappearance of the symptoms of radiation sickness. Depression, weakness, and asthenia persist for a long period of time. In treating patients of the first groups, who have radiation sickness as a result of exposure to prolonged but weak irradiation, an indispensable condition is temporary interruption or complete cessation of the work which resulted in exposure to radiation. Often this alone suffices in order that health be restored. Treatment in a sanitarium, taking of vitamins, and hydrotherapy are recommended.

Whenever persistent changes of the morphological composition of the blood have taken place, it is necessary to carry out single or multiple blood transfusions and to administer antianemin and iron. The treatment of patients who have been subjected to radiation therapy is much more difficult. One must take into consideration in connection with this that the prophylaxis of radiation sickness is more effective than therapy of this condition once it has reached the acute stage. Thus, transfusion of blood prior to radiation therapy, if it is systematically carried out during the course of treatment with radiant energy, may prevent the development of radiation sickness. On the other hand, blood transfusions are not very effective after radiation sickness has actually set in. Prophylaxis of radiation sickness must include measures for preventing local reactions in the tissues being irradiated as well as measures which improve the general condition of the patient.

Measures which bring about anesthesia and anemia of the tissues being irradiated have proved most effective in reducing local reactions. These measures comprise tieing up of blood vessels, a novocain block, use of novocain together with adrenalin, etc.

In order to counteract general phenomena one applies measures which restore the equilibrium of the nervous system (administration of bromides and caffeine) and measures which stimulate the organs of hemopoiesis. The latter comprise administration of tezan, folic acid, and antianemin; transfusion of blood or plasma; administration of vitamins; and a number of other measures.

The therapy of acute radiation sickness presents great difficulties. First aid consists in removing the patient from the zone where he is exposed to radiation, sanitary treatment, and assurance of complete physical and moral rest, using for this purpose anesthetics or hypnotics [literally "narcotics"], if necessary. A special diet is prescribed. This diet must be liquid in the beginning, while later on, depending on the condition of the gastrointestinal tract, it may be liquid or of ordinary consistency. The food must have a high calorie content and be particularly rich in proteins. The amount of carbohydrates must be reduced to a minimum, in order to reduce as far as possible the formation of gas and not to overload or irritate the mucous membranes of the intestine because large amounts of roughage must be eliminated.

It is not recommended to give too much fat. On the other hand, it is desirable to increase the intake of vitamins by giving the patient fruit juice and fresh fruit. If the patient refuses to eat, nutrition must be maintained by recourse to parenteral administration of foodstuffs. Dehydration should be prevented by taking ordinary measures, namely transfusion of blood or plasma and injection of isotonic solutions. It is extremely important to give proper care to the patients and in doing this to observe the general rules of hygiene, taking proper care of the skin and of the mucous membrane of the mouth, and preventing the formation of lesions.

Medical care should not be interrupted even after recovery.

Transfusion of blood is necessary because of the interruption of hemopoiesis, which is brought about by injury of the bone marrow. It is also necessary in order to compensate for the loss of blood due to hemorrhages. Finally, blood transfusion is invaluable for the treatment of shock brought about by exposure to radiation. Transfusion of blood should take place at a relatively early stage of radiation sickness. One usually administers 250 millimeters every 4 days for 6 weeks.

Among drugs to be used in combatting infection, penicillin occupies the most important place. Compounds of penicillin which are eliminated slowly from the organism are particularly useful, because injections can be carried out over long intervals, so that the necessity of inflicting superfluous trauma is eliminated. Penicillin should be introduced as a prophylactic agent in a quantity of 300,000 units every second day. If infection with gram-negative bacteria takes place, one must use chloromycetin and streptomycin. In order to avoid the development of a resistance to streptomycin, this antibiotic should be used for therapeutic purposes only and not for prophylaxis.

It is recommended that in addition to penicillin aureomycin and terramycin be used. In view of the fact that the majority of sulfonamides exert a slightly toxic effect, they should be used only in special cases.

The tendency toward hemorrhages which the patients develop is due on the one hand to an excess of heparin over its normal content in the blood, so that coagulation is prevented and destruction of thrombocytes interfered with. On the other hand, the tendency to develop hemorrhages is due to injuries sustained by the walls of the blood vessels. To counteract heparinemia one must apply toluidine blue and protein sulfate. The latter is a particularly good remedy. After its application, satisfactory results are obtained: hemorrhages often cease and the capacity of the blood to coagulate gradually returns to normal.

In order to counteract the fragility of capillaries, the use of antihistaminic drugs has been proposed, namely of benadryl and desoxycorticosterone.

Vitamin C reduces the fragility of the walls of capillaries and furthermore reduces the time of blood coagulation. For therapy eliminating the increased fragility of capillaries, one may also recommend rutin, vitamin P, and various flavones.

If anemia developes, profuse transfusions of whole blood or of erythrocytic mass are recommended.

Various drugs to be administered for prophylactic purposes have been proposed lately. Among them is cysteamine (beta-mercaptoethylamine or "becaptan"). It has been shown experimentally that administration of this drug to mice 1-3 minutes prior to irradiation contributes to a higher percentage of survival among these animals. On the other hand, if the drug is administered 0.5-3 minutes after irradiation, no protective effect is apparently exerted. It has been established in histological work that the primary injuries are the same both in experimental animals [which have received the drug] and control animals. However, regeneration takes place more rapidly in animals which have received cysteamine.

Observations made by foreign investigators show that the intravenous injection of 200 milligrams of cysteamine to patients suffering from radiation sickness is sufficient to eliminate the symptoms of this sickness.

A great number of other drugs recommended by foreign investigators for the prophylaxis of radiation sickness proved to be little effective after being checked.

The problem of the prophylaxis and therapy of acute forms of radiation sickness cannot be regarded as solved at the present time. The aspects of radiobiology pertaining thereto should be subjected to further study.

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